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Award Number: W81XWH-04-1-0769

TITLE: A Phase II Trial of Androgen Suppression and Radiation Therapy with Samarium-153 in Localized, High-Risk, Prostate Cancer

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REPORT DATE: August 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
01-08-2005	Annual	30 Jul 2004 – 29 Jul 2005

4. TITLE AND SUBTITLE
A Phase II Trial of Androgen Suppression and Radiation Therapy with Samarium-153 in Localized, High-Risk, Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-04-1-0769

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Thomas Jefferson University
Philadelphia, PA 19107-5567

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
No abstract provided.

15. SUBJECT TERMS
No subject terms provided.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	6	19b. TELEPHONE NUMBER *(include area code)*

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Subject: Report for Award Number W81XWH-04-1-0769

Title: A Phase II trial of Androgen Suppression and Radiation Therapy with Samarium-153 in Localized, High-Risk, Prostate Cancer

Clinical Trial Development Award (PC040944)

The purpose of this award was to develop the above trial along with its implementation. In addition, the funding supported the submission for a Clinical Trial Award proposal to the Department of Defense Granting Agency that was submitted, as required, in December, 2004. This involved the formation of a clinical protocol, informed consent, and data submission forms. Under the terms of the Clinical Trial Development Award, basic or clinical research was not permitted so I do not have any data to report.

As stated in my SOW, we carried out an extensive medical literature review to determine appropriate patient population and sample size.

The design and statistical methods for this multi-institutional phase II clinical trial were developed in collaboration with the Director of Biostatistics Shared Resource of the Kimmel Cancer Center (KCC) at Thomas Jefferson University, **Dr. Walter Hauck**.

The **primary objective** of this multi-institutional phase II clinical trial was to document the ability of samarium-153, when given with neoadjuvant HT and RT, to inhibit the development of disease progression as compared to historical controls.

The primary clinical endpoint was proposed to be time to disease progression. We defined the failure event for PFS as the first occurrence of distant failure, regional failure, local progression, biochemical progression, or death as a result of any cause. This definition of PFS is similar to that used in RTOG 94-13 (1). We defined biochemical progression according to the ASTRO consensus definition (2).

Time to disease progression was proposed to be analyzed using survival analysis techniques to compare two groups in a 2 to 1 ratio: *historical controls treated with neoadjuvant HT and RT* to *experimental group treated with neoadjuvant HT, RT* and the *addition of samarium-153*. Specifically, PFS will be estimated using the Kaplan-Meier method and the comparison of the two groups will be made by the log-rank test **(p=0.05, 2-sided test).** Historical controls will be identified at each study site with the control to experimental sample size ratio of 2:1.

We estimated to accrue 8-10 patients at each of 10 sites (a multi-institutional study was decided) during 9 to 12 month accrual period. We were aiming at a target accrual of 96 patients. The patients were to be followed for 2 years after date of study entry, resulting in study duration of 2.75-3 years. Power computations were completed for a 2-sided log-rank test to detect a 15% absolute difference in 2-year PFS rates between experimental

and control groups, assuming exponential event rates, one year accrual period with two year follow-up, and α=0.05.

From our literature review, we assumed an expected 2-year PFS rates in the control group between 74-78%, and 2 controls per 1 experimentally treated patient. The power computations suggestd at least 92% power to test the primary hypothesis if the accrual goal of **96 patients and 192 controls** is met.

Exploratory statistical analyses was developed to investigate association between the bone remodeling factors (**urinary NTx and Dpd, and serum OC and BAP**) and PSA and clinical outcome. Cox proportional hazard models was planned in order to examine the relationship between the primary and secondary endpoints and the bone biomarkers. The bone remodeling factors would have been measured repeatedly after samarium-153 and included in the Cox model as time-dependent covariates. Association between PSA level and bone biomarkers was to be evaluated in a mixed effects linear model, which is suitable to accommodate longitudinal data with repeated measurements on PSA level and bone biomarkers. Also, a longitudinal mixed effects linear model was considered for bone factors to investigate their long-term behavior and response to bone-targeted therapy with samarium-153. All models were to be fitted controlling for known prognostic factors, such as tumor stage, Gleason score, and baseline PSA. Statistical analyses was to be performed using SAS 9.0 (SAS Institute, Inc., Cary, NC) and S-Plus (Insightful, Seattle, WA).

As initially proposed, the clinical protocol and associate forms were developed with assistance of the TJU Departmental Senior Clinical Research Coordinator, **Ms. Roseann Bonanni.** The clinical protocol and consent forms were developed according to the DOD HSRRB-approved template for clinical protocols. Internal case report forms were developed to obtain the data necessary for achieving the protocols objectives.

The protocol was approved after review by the Clinical Cancer Research Review Committee at the KCC. The protocol and consent forms are currently under review by the TJU IRB and the human use committee of the Radiation Safety Office. We were planning on using a real-time clinical trial registration and data management system. This system will be based on web-site modules that are being developed with **Vish Iyer, M.S.**, Director of Information Systems for the American College of Radiology (ACR).

This phase II trial was developed to be conducted as a national multi-institutional study at 10 clinical sites. The 10 sites were selected because of **access to prostate cancer patients** and previous success in enrolling patients on prostate cancer clinical trials. None of the sites have clinical trials competing for high-risk patients. Three of the sites (TJU Hospital, Frankford Hospital, and Christiana Care Health Services) belong to the Jefferson Oncology Group Cancer Network. This group has access to a diverse prostate cancer patient population of nearly 1000 newly diagnosed cancer cases in the tri-state region. Six (**in bold below**) of the 10 sites are among the RTOG top 12 **United States of America** accruers to prostate cancer clinical trials, with all sites having excellent data quality scores for study subject retention and follow-up (ACR personnel communication).

All the site investigators provided **letters of intent,** stating access to the appropriate prostate cancer population, assurance to recruit 8-10 patients within one year, and agreement with proposed patient enrollment and specimen handling budget, and agreement with the **Intellectual Property Plan.**

We developed the **Intellectual Property Plan** with the Office of Technology Transfer (OTT) at TJU. It is the policy of TJU to comply with all applicable regulations and requirements of any sponsored work at the University, regardless of whether that research is funded by the government, industry, foundation, or other sponsors. The TJU Patent Policy can be found at http: //www.jefferson.edu/universitycounsel/ policies.htm.

Unfortunately, we were not awarded the Clinical Trial Award to carry out this developed clinical trial and will seek other sources of funding.

1) Roach, M., Lu, J., Lawton, C., Machtey, M., Seider, M., Rotman, M., Jones, C., Asbell, S., Valicenti, R.K., Han, S., Thomas, C., Shipley, W. A phase III trial comparing whole-pelvis (WP) versus prostate only (PO) radiotherapy and neoadjuvant versus adjuvant total androgen suppression (TAS): preliminary analysis of Radiation Therapy Oncology Group (RTOG). J Clin Oncol. 21 (10): 1904-1911, 2003.

2) Cox J, Grignon D, Kaplan R, et al: Consensus statement: Guidelines for PSA following radiation therapy. Int J Radiat Oncol Biol Phys 37: 1035-1041, 1997.